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See editorial comment on page 2154

On the basis of the benefits of antihypertensive treatment, progressively intensive treatment is advocated. However, it remains controversial whether intensive blood pressure control might increase the frequency of serious adverse events (SAEs) compared with moderate control. This review assessed the occurrence of SAEs in blood pressure treatment with predefined blood pressure targets. Seven original studies and eight post hoc analyses (derived from two original studies) met the inclusion criteria. Compared with moderate blood pressure treatment, intensive treatment was associated with a significant increase in treatment-related SAEs (Sign-test: $P = 0.0002$, Wilcoxon signed-rank test: $P = 0.001$). However, comparability between studies was limited, due to unclear determinations about the treatment-relatedness of adverse events, missing definitions of SAEs and variations in recording methods. Thus, a meta-analysis was not justified. The definitions of serious adverse events and methods of recording and reporting need to be improved and standardized to facilitate the comparison of results.

Keywords: blood pressure determination, blood pressure treatment, hypertension, intensive, moderate, serious adverse events

Abbreviations: AASK, African American Study of Kidney Disease and Hypertension; ACC, American College of Cardiology; ACCORD, Action to Control Cardiovascular Risk in Diabetes Trial; AHA, American Heart Association; AKI, Acute Kidney Disease; Cardio-Sis, CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica; CDK, Chronic kidney disease; eGFR, estimated glomerular filtration rate; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; JATOS, Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Ana; RCT, randomized controlled trial; SAE, serious adverse event; SIGN, Scottish Intercollegiate Guidelines Network; SPRINT, Systolic Blood Pressure Intervention Trial; SPS3, Secondary Prevention of Small Subcortical Strokes Trial; VALISH, Valsartan in Elderly Isolated Systolic Hypertension Study

INTRODUCTION

Worldwide, arterial hypertension affects about 1.39 billion people [1]. The diagnosis of high blood pressure is often delayed, due to its typically asymptomatic course. Arterial hypertension is the most common modifiable risk factor of death in men, and the second most common in women. Untreated hypertension increases the risk of ischemic, coronary and hypertensive heart diseases; ischemic and haemorrhagic stroke; and chronic kidney disease [2,3]. The risk of a cardiovascular event with systolic hypertension is highly correlated with age. The prevalence rises with increasing age, up to 60–70% among individuals over 60 years old [4].

Antihypertensive therapy reduces the risk of cardiovascular and cerebrovascular events [5–7]. However, a relevant issue in hypertension treatment is the difficulty in determining the degree of blood pressure lowering. Extensive meta-analyses have suggested that 'the lower [the blood pressure], the better' [8]. Large-scale trials that investigated the efficacy of lowering blood pressure showed that risk could be reduced by up to 22% for coronary heart disease and 40% for stroke, with a 10-mmHg reduction in blood pressure [9,10]. However, defining the optimal blood pressure target range is challenging, because the effect on risk follows a 'J-shaped curve', wherein more harm than benefit is incurred at very low blood pressure levels [11–13].

In 2017, the American College of Cardiology/American Heart Association (ACC/AHA) recommended that the target blood pressure should be below 130/80 mmHg, except in patients who require secondary stroke prevention and patients with low cardiovascular risk; in the latter cases, a target level of less than 140/90 mmHg was advised [14]. Lower blood pressure targets require an extensive therapy regime, and the risk of adverse events increases [15]. Adverse events can be a direct effect of the antihypertensive agent (e.g. angioedema, cough, rash) or a consequence of low blood pressure (e.g. hypotension, syncope). Antihypertensive treatment in the older population is

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particularly challenging, due to comorbidity, frailty, polypharmacy and cognitive impairments. In this population, a single serious adverse event, such as a syncope, could have major consequences; thus, a very strict blood pressure-regime might not be adequate, and higher blood pressure levels can be tolerated [14]. Few meta-analyses have focused on the frequencies of adverse events at different blood pressure targets [7,16,17].

In this review, we analysed results from randomized studies to assess the frequencies of various serious adverse events associated with blood pressure target-level oriented therapies.

MATERIALS AND METHODS

This systematic review was designed according to the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) [18].

Literature search

In April 2018, a systematic literature search was conducted by an experienced librarian (M.G.) at Careum Bibliothek of the University of Zurich. The following six databases were included: MEDLINE (via Ovid), EMBASE, Cochrane Library, Web of Science, Scopus and Pool. The search terms used were 'intensive, strict, aggressive, tight, standard, moderate blood pressure control', 'target blood pressure', 'adverse events' and 'side-effects'. A detailed description of one search strategy is shown in Supplementary Table 1, http://links.lww.com/HJH/B119. No search limitations were applied, in terms of the type of study, publication date or language. Reference lists from reviews and meta-analyses were manually scanned to identify any other relevant studies.

Inclusion criteria

We included randomized trials that compared the results between two groups of patients with hypertension that had different blood pressure targets. Eligible studies had to include at least 30 patients with arterial hypertension aged 18 years or older, and they had to assess target-oriented blood pressure treatment that consisted of various pharmacological agents, given at various dosages, and the doses were titrated until the patient achieved the target blood pressure levels.

Studies that compared antihypertensive agents or different dosages were excluded when they lacked predefined blood pressure targets, quantification of adverse events or baseline characteristics. Furthermore, studies were excluded when they focused on secondary antihypertensive treatments (e.g. bariatric surgery, diet, reduced salt intake), blood pressure treatment in emergency situations (e.g. intracerebral haemorrhage, pregnancy, hypertensive emergency) or treatment in perioperative settings. Trials were excluded when they assessed cotreatments in addition to antihypertensive treatment (e.g. treatments for diabetes mellitus, dyslipidaemia) with defined targets [e.g. HbA1c $<7\%$, low-density lipoprotein (LDL)-level <1.8 mmol/l], due to the lack of a clear association between adverse events and the antihypertensive treatment.

Study selection

The identification of eligible publications, data extraction and quality assessments were conducted independently by two authors (LF and JB). All references were initially screened for relevance, based on the title and abstract, by two reviewers (LF and JB). Finally, full text analyses were performed to determine eligibility. Disagreements were discussed and resolved by consensus or with third party arbitration (JS).

Quality assessment

We used the checklist of the Scottish Intercollegiate Guidelines Network (SIGN) for randomized controlled trials (RCTs) [19] to assess the quality of included RCTs. Study quality criteria included proper randomization conduct, treatment allocation concealment, similarity of treatment groups at baseline, a description of study eligibility criteria, completed follow-up, bias minimization and the use of an intention-to-treat analysis. A high-quality rating was given when the majority of criteria were fulfilled and further research would have been unlikely to contradict study results; an acceptable quality rating was given when most criteria were met with a few flaws, and future research might reduce the certainty of the conclusions. A low-quality rating was given when either most criteria were not met or significant flaws were present in key aspects of the study design.

Data extraction

For each trial, standard information was extracted into a Microsoft Excel (2016) spreadsheet (Microsoft Corporation, Redmond, Washington, USA). The standard data included baseline patient characteristics [age, sex, BMI, smoking status, mean SBP and DBP, history of diabetes, estimated glomerular filtration rate (eGFR), history of cardiovascular event, statin use], blood pressure targets in each study arm, the follow-up duration, the mean SBP and DBP during the trial, outcome events and serious adverse events.

Definition of moderate and intensive treatment

We defined in each study 'moderate' as the treatment group with the higher SBP target and the 'intensive' as the lower SBP target.

Outcomes

The outcomes of interest were the frequency of adverse events, particularly serious adverse events, during antihypertensive treatment with different blood pressure targets. According to the Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, document E2A), a serious adverse event was defined as a harmful side effect that is fatal or life threatening, results in clinically significant or persistent disability, or requires or prolongs hospitalization [20]. Because a 'side effect' suggests causality between a treatment and a harmful event, which can rarely be confirmed, the term 'adverse event' was more suitable, according to a recommendation from the CONSORT Statement extension [21].

Statistical analysis

The primary objective of this study was to assess the frequency of adverse events during pharmacological treatments for arterial hypertension that targeted predefined blood pressure levels. We analysed all adverse events and treatment-related adverse events. Because most secondary studies (i.e. secondary analyses from original studies) were derived from the Systolic Blood Pressure Intervention Trial (SPRINT) [6], the results were not independent, due to the partially overlapping patient subgroups; thus, a meta-analysis would not have been justified. Therefore, we performed only descriptive and comparative analyses to summarize findings across all studies. The nonparametric Sign-test and Wilcoxon signed-rank test were performed to compare distributions of adverse events between intensive and moderate treatment groups. The Wilcoxon signed-rank test takes into consideration the magnitude of the difference between population means.

Our secondary objective was to identify potential subgroups that were at an increased risk of serious adverse events, based on secondary studies that analysed the population from the SPRINT study [6].

All analyses were performed with R statistical software (R Core Team, Vienna, Austria) [22].

RESULTS

Study selection

Our systematic literature search yielded 1805 studies, and 932 remained after removing duplications (Fig. 1). Checking the reference lists of identified studies revealed 11 additional publications; therefore, we assessed a total of 943 studies for title and abstract relevance. On the basis of relevant titles and abstracts, we assessed 65 publications in detail and applied all inclusion and exclusion criteria. The main reasons for exclusion are shown in Fig. 1. Finally, 15 studies were included in the present review. A quality assessment of the studies did not lead to any other exclusions.

Overview of included studies

Of the 15 included studies, six were original trial reports [6,23–27] and nine were secondary analyses [28–36]. One of the secondary analyses describes a trial whose original report (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients, JATOS [37]) was excluded due to insufficient quantitative data. Consequently, we treated the secondary per-protocol analysis (JATOSpp [28]) of that trial as an original study, due to an extensive analysis of serious adverse events.

The characteristics of the included seven original studies are summarized in Table 1. All studies were conducted in an outclinic setting with patients who were not institutionalized, and all studies were published between 2002 and 2015. The mean participant age ranged from 54 to 76 years, and follow-up periods ranged between 2 and 4.7 years. The follow-up in the SPRINT study lasted until August 2015; the trial was terminated early, due to significant interim results that favoured the intensive intervention [6]. In the different study arms, the SBP targets varied between 120 and 160 mmHg.

Eight secondary studies were included that were posthoc analyses of the original studies. Of these secondary studies, seven were derived from the SPRINT study [30–36], and one was derived from the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD) [29]. Baseline characteristics are described in Table 1.

Characteristics of original studies

Only some studies considered whether adverse events were treatment related. The SPRINT trial reported all adverse events together, and then separately studied possible treatment-related and definite treatment-related groups [6]. The ACCORD [24] and Secondary Prevention of Small Subcortical Strokes Trial (SPS3) [26] trials only reported adverse events that were possibly related to antihypertensive treatment. No information concerning treatment relatedness was provided in the African American Study of Kidney Disease and Hypertension (AASK) [23] or JATOSpp [28] study. None of the trials documented the same set of adverse events.

Methods for recording serious adverse events varied between studies (Table 1). Five studies [6,23–25,27] used clinic visits for recording serious adverse events, two of them conducted a structured interview [6,23]. In two studies, no details were available about the recording method [26,28]. After titrating the medication to achieve the target blood pressure, the frequency of clinic visits were set to at least once a month [23,24,26], at least every 2 months [6], every 3 months [27], every 4 months [25] and at least two times per year [28]. More information about the reviewed studies is provided in Supplementary Tables 3 and 4, http://links.lww.com/HJH/B119.

To achieve predefined blood pressure targets, all studies used a treatment algorithm. The algorithm prescribed the dose titration and the addition of drugs, based on a stepwise approach. The choice of agents in each pharmaceutical class was determined by the trial investigators. In the AASK trial [23], participants were randomized to a β-blocker (metoprolol), angiotensin-converting enzyme inhibitor (ramipril) or the dihydropyridine calcium channel blocker, amlodipine, but further open-label agents were added to achieve the target blood pressures. On the contrary, the JATOSpp [28] and Valsartan in Elderly Isolated Systolic Hypertension Study (VALISH) [27] trials started with efonidipine or valsartan, followed by dose titration, and then other agents were added.

We compared the changes in blood pressure due to the different treatment regimes employed in the reviewed studies (Fig. 2). For example, in the ACCORD study, the target values were 120 and 140 mmHg for intensive and moderate treatments, respectively. The mean baseline systolic pressures were 130.0 and 139.4 mmHg, respectively. The mean blood pressures achieved were 119.3 and 133.5 mmHg, respectively. However, the achieved blood pressures were measured differently among studies. One study measured the postbaseline average over 3 months [23] and other studies measured blood pressure after 1 year of follow-up [6,24–28]. Only four studies [24,26–28] actually achieved the predefined target in the intensive treatment group after 1 year of target-oriented treatment.

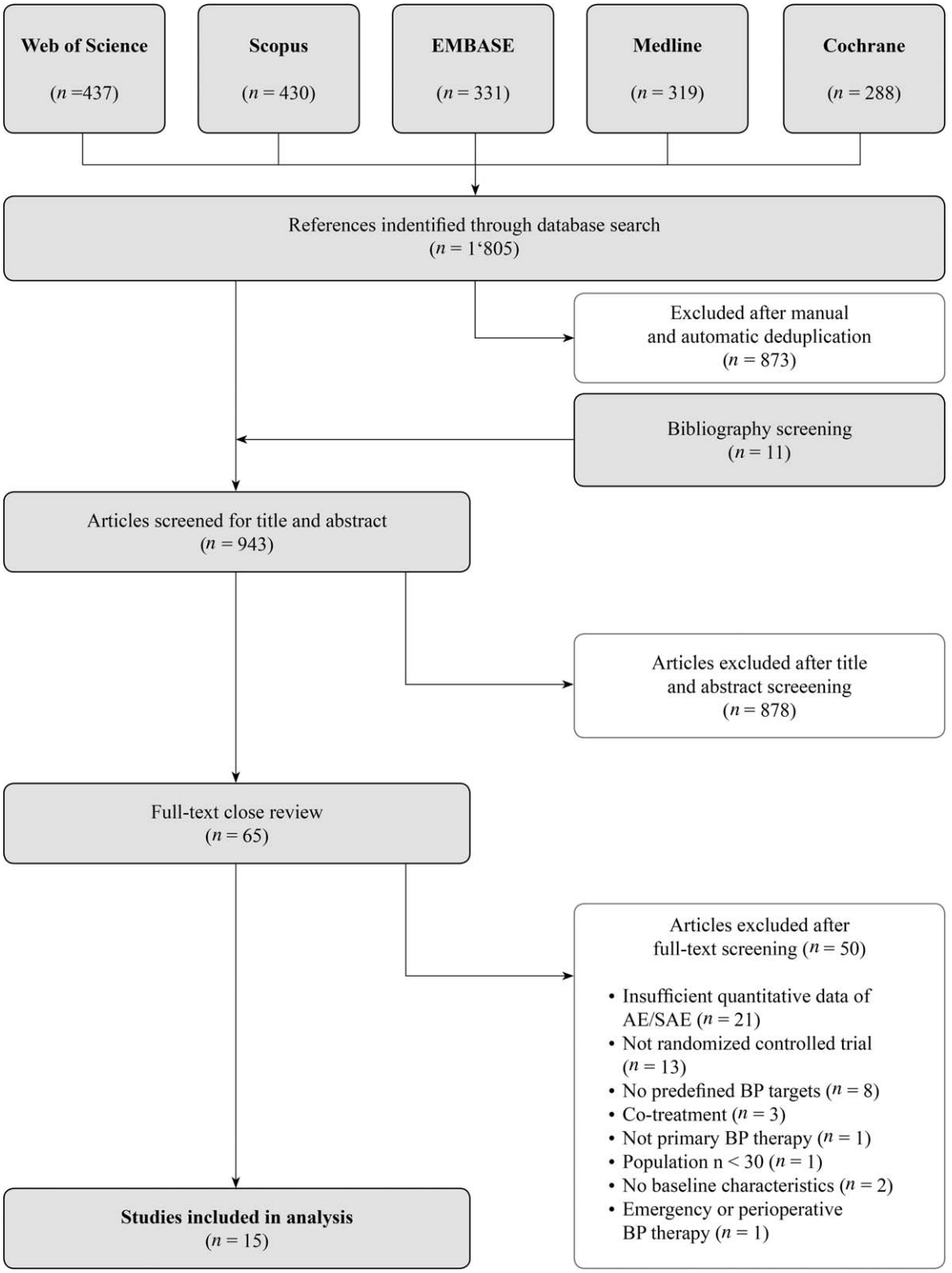

FIGURE 1 Flowchart of study selection. AE, adverse event(s); BP, blood pressure; SAE, serious adverse event(s).

Definition of serious adverse events

Only the ACCORD [24] and SPRINT [6] studies provided a definition of serious adverse events that conformed to the definition from the ICH Working Group [20]. All the other studies had unclear definitions of serious adverse events (Supplementary Table 3, http://links.lww.com/HJH/B119).

Moreover, often, each particular serious adverse event was either not clearly defined or not reported. In the SPRINT study [6], hypotension was defined as a

TABLE 1. Baseline characteristics of all eligible studies

Study	Year	Mod. vs. int. SBP targets (mmHg)	Secondary analysis of	Participants	Age (years); mean (SD)	Follow-up (years); (median)	Recording method of serious adverse events	Serious adverse events reported
Original studies								
ACCORD [24]	2010	120 vs. 140	–	4733	62.2 (6.9)	4.7[b]	Clinic visit	Hypotension, syncope, bradycardia/arrhythmia, hyperkalaemia, angioedema, acute kidney injury, swelling/hives, dizziness
SPRINT [6]	2015	120 vs. 140	–	9361	67.9 (9.5)	3.3	Clinic visit, structured interview, ER reports	Hypotension, syncope, injurious fall, bradycardia, electrolyte abnormalities, hyperkalaemia, acute kidney injury, dizziness
SPS3 [26]	2013	130 vs. 150	–	3020	63.0 (10.8)	3.7[b]	NR	Syncope, injurious fall, dizziness, light-headedness, stroke, blurred vision, unsteadiness
VALISH [27]	2010	140 vs. 150	–	3079	76.1 (4.1)	3.1	Clinic visit, report forms for SAE	Acute kidney injury
Cardio-Sis [25]	2009	130 vs. 140	–	1111	67.0 (7.0)	2	Clinic visit/ telephone calls	Hypotension, angioedema, swelling/hives, dizziness, diarrhoea, asthenia, coughing
AASK [23]	2002	<92 vs. 102–107[a]	–	1094	54.6 (10.6)	4	Clinic visit, structured interview	Syncope, hyperkalaemia, angioedema, dizziness, light–headedness, dyspnoea, oedema, coughing
JATOSpp [28]	2010	140 vs. 160	JATOS [32]	2722	73.5 (5.2)	2	NR	Fractures, dizziness, light-headedness
Secondary studies								
Margolis *et al.* [29]	2014	120 vs. 140	ACCORD [33]	3099	62.6 (6.6)	3.5[b]/4.5[c]	Clinic visit, structured interview	Falls, fractures
Beddhu *et al.* [30]	2017	120 vs. 140	SPRINT [6]	6662	66.6 (9.0)	3.3	Clinic visit, structured interview, ER reports	Albuminuria, CKD event
Bress *et al.* [31]	2017	120 vs. 140	SPRINT [6]	9323	67.9 (9.4)	3.3	Clinic visit, structured interview, ER reports	Hypotension, syncope, injurious fall, bradycardia, electrolyte abnormalities, hyperkalaemia, acute kidney injury, dizziness
Cheung *et al.* [32]	2017	120 vs. 140	SPRINT [6]	2646	72.0 (9.3)	3.3	Clinic visit, structured interview, ER reports	Hypotension, syncope, injurious fall, bradycardia, electrolyte abnormalities, hyperkalaemia, acute kidney injury, dizziness
Foy *et al.* [33]	2017	120 vs. 140	SPRINT [6]	9361	67.9 (9.5)	3.3	Clinic visit, structured interview, ER reports	Hypotension, syncope, injurious fall, bradycardia, electrolyte abnormalities, hyperkalaemia, acute kidney injury, dizziness
Obi *et al.* [34]	2017	120 vs. 140	SPRINT [6]	9324	67.7 (9.0)	3.3	Clinic visit, structured interview, ER reports	Albuminuria, eGFR outcome, acute kidney injury
Still *et al.* [35]	2018	120 vs. 140	SPRINT [6]	9185	67.9 (9.0)	3.3	Clinic visit, structured interview, ER reports	Hypotension, syncope, injurious fall, bradycardia, electrolyte abnormalities, acute kidney injury, dizziness
Williamson *et al.* [36]	2016	120 vs. 140	SPRINT [6]	2636	79.9 (4.0)	3.3	clinic visit, structured interview, ER reports	Hypotension, syncope, injurious fall, bradycardia, electrolyte abnormalities, acute kidney injury, dizziness

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ER, emergency room; int., intensive antihypertensive treatment; mod., moderate antihypertensive treatment; NR, not reported; SD, standard deviation.
[a]Mean arterial pressure; alternative values for follow-up periods.
[b]Mean.
[c]Mean for falls/fractures.

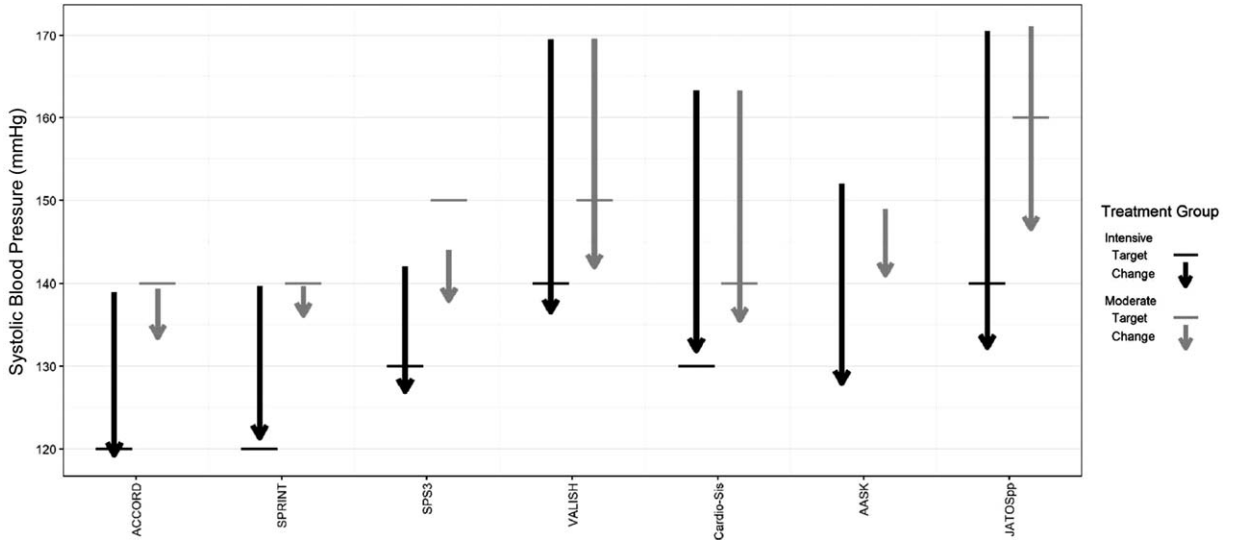

FIGURE 2 Comparison of target and achieved blood pressures results from seven studies. Arrows show the changes in systemic blood pressure with moderate (grey) and intensive (black) treatments. The beginning of each arrow indicates the baseline mean SBP; the tip of each arrow demonstrates the achieved mean SBP. Horizontal lines are the targeted values. The AASK trial target values are not illustrated, because the targets were expressed for the mean arterial pressure, rather than the SBP.

symptomatic low blood pressure without specific blood pressure cut-offs; syncope was a sudden temporary loss of consciousness; and an injurious fall was a fall that resulted in either an emergency department evaluation or hospitalization. Acute kidney injury (AKI) was reported when it was listed in the hospital discharge summary or noted in the emergency department [6]. In the VALISH study [27], an AKI was defined as a doubling of serum creatinine to a level more than 2.0 mg per 100 ml or the introduction of dialysis.

Frequency of serious adverse events in original studies

Table 2 summarizes the serious adverse events in original studies reported for the corresponding treatment groups. The frequencies of adverse events varied greatly between the different studies. In studies wherein the serious adverse events were attributed to treatment [6,24,26], a significantly higher rate of serious adverse events was related to intensive blood pressure therapy compared with moderate therapy (Sign-test: $P = 0.0002$, Wilcoxon signed-rank test: $P = 0.001$). In studies that did not differentiate between treatment-related and nontreatment-related serious adverse events [6,25,27], a significant increase in serious adverse events was noted with intensive treatment compared with moderate treatment, when the rates of serious adverse events were compared with the Wilcoxon-test ($P = 0.01$), but not with the Sign Test ($P = 0.12$). On the contrary, in studies that provided no information about the relationship between serious adverse events and antihypertensive treatment [23,28], no significant difference in adverse events was observed between the intensive and moderate treatment groups (Sign-test: $P = 1.0$, Wilcoxon signed-rank test: $P = 0.13$).

In the groups with intensive blood pressure treatment, the rates of dizziness varied from 0.1% [28] to 53.4% [23] and

TABLE 2. Frequencies of serious adverse events in original studies (in %)

	Group	attr.	Dizziness	Hypo-tension	Syncope	Injurious falls	Fractures	AKI	Angio-edema	Hyper-kalaemia	Coughing	Brady-cardia
ACCORD [24]	int.	Yes	43.3	0.7	0.5	–	–	23.8	0.3	3.1	–	–
($n = 4733$)	mod.	Yes	40.3	0.0	0.2	–	–	15.5	0.2	3.0	–	–
SPS3 [26]	int.	Yes	21.6	–	0.7	0.2	–	–	–	–	–	–
($n = 3020$)	mod.	Yes	20.0	–	0.3	0.0	–	–	–	–	–	–
Cardio-Sis [25]	int.	No	0.4	0.9	–	–	–	0.2	–	–	2.5	–
($n = 1111$)	mod.	No	0.7	0.4	–	–	–	0.2	–	–	1.3	–
AASK [23]	int.	–	53.4	–	6.3	–	–	–	3.5	0.0	54.6	–
($n = 1094$)	mod.	–	49.0	–	5.2	–	–	–	5.4	0.7	47.0	–
JATOSpp [28]	int.	–	0.1	–	–	–	0.5	–	–	–	–	–
($n = 2722$)	mod.	–	0.5	–	–	–	0.6	–	–	–	–	–
SPRINT [6]	int.	Yes	–	2.7	2.0	0.8	–	2.1	–	3.8	–	1.1
($n = 9361$)	mod.	Yes	–	1.2	0.9	0.5	–	0.8	–	3.7	–	0.6
SPRINT [6]	int.	No	–	3.4	3.5	7.1	–	4.4	–	–	–	2.2
($n = 9361$)	mod.	No	–	2.0	2.4	7.1	–	2.6	–	–	–	1.8
VALISH [27]	int.	No	–	–	–	–	–	0.3	–	–	–	–
($n = 3079$)	mod.	No	–	–	–	–	–	0.1	–	–	–	–

–, not reported; AKI, acute kidney injury; attr., attributable to antihypertensive treatment; int., intensive antihypertensive treatment; mod., moderate antihypertensive treatment.

hypotension, syncope and injurious falls occurred more commonly than fractures. It was difficult to compare groups in terms of AKI, due to nonuniform definitions and varying frequencies. The ACCORD trial [24] defined AKI in terms of absolute creatinine elevations (>1.5 mg/dl in men, >1.3 mg/dl in women). In contrast, the SPRINT trial [6] determined acute kidney injuries, based on hospital discharge summaries and emergency reports. Nevertheless, higher rates of renal events were observed among patients who received intensive treatment compared with patients who received moderate treatment. Varying results related to the frequency of coughing were observed in the CARDIOvascolari del Controllo della Pressione Arteriosa SIStolica (Cardio-Sis) and AASK studies [23,25]. Additional details about serious events are shown in Supplementary Table 5, http://links.lww.com/HJH/B119.

Frequency of serious adverse events in secondary studies

Results from secondary studies are illustrated in Supplementary Table 6, http://links.lww.com/HJH/B119. Generally, the secondary studies reported increased rates of serious adverse events associated with intensive treatment. Most studies reported about AKI, and except for Obi *et al.* [34] and Margolis *et al.* [29], all reported about hypotension, syncope, injurious falls, bradycardia and electrolyte abnormalities. Further, there is some evidence to suggest that intensive treatment had lower risk of injurious falls, especially among patients aged more than 75 years. Beddhu *et al.* [30] reported a significant higher risk for incident of chronic kidney disease (reduction in eGFR of at least 30% with a confirmed level less than 60 ml/min/1.73 m^2) in the intensive treatment group.

Risk of bias

The assessment of the risk of bias, based on the SIGN Checklist for randomized controlled studies, is shown in Supplementary Table 2, http://links.lww.com/HJH/B119. All studies were at least acceptable in their effort to minimize bias; therefore, no study was excluded. No study implemented blinding of individuals or investigators; thus, potential performance and detection biases could not be ruled out.

DISCUSSION

Main findings

This study reviewed the results of seven randomized original trials with 25 120 participants to assess adverse effects of treatments with different blood pressure targets. We found that serious adverse events significantly increased in treatments with lower blood pressure targets. Despite the cardiovascular benefit, intensive antihypertensive treatment was associated with significantly elevated frequencies of dizziness, syncope, AKI and hypotension compared with moderate antihypertensive treatment. In secondary studies, the risk of injurious falls did not appear to be associated with more intensive blood pressure treatment; this is in contrast to the results for all other types of serious adverse events. A meta-analysis of the results was not feasible, due to methodological heterogeneity among the original studies. These studies used different definitions of adverse events; different methods of recording adverse events; different blood pressure targets; variable follow-up times; and diverse study populations.

Comparison to existing literature

To the best of our knowledge, this is the first systematic review to present data on the entire spectrum of serious adverse events reported in studies that evaluated the benefits and adverse events between moderate and intensive blood pressure treatment modalities. Previous publications performed limited investigations of the benefit–harm ratio of antihypertensive treatments. They only compared the rate of cardiovascular events and the total number of all serious events [16,17], or they analysed only specific adverse events (e.g. syncope, hypotension, falls, cognitive outcome or acute kidney injuries) [7,29,38,39]. Weiss *et al.* [7] and Sink *et al.* [39] confirmed the associations between low blood pressure targets and increased risks of hypotension, syncope and a higher medication burden. In a meta-analysis from Bangalore *et al.* [16], the risk of any serious adverse event was elevated in patients with low blood pressure targets (<120 and <130 mmHg), compared with those with higher targets, but they did not specify the rates of particular serious adverse events.

To date, age has not been associated with an increase in the risk of serious adverse events in antihypertensive therapy. However, serious adverse events have been reported to be insignificantly higher in older than in younger individuals [36]. Other risk factors associated with an increase in adverse effects with antihypertensive treatment have included smoking, statin treatments, elevated creatinine and lipid levels [15], elevated pulse pressure [40] and a high visit-to-visit variability in DBP [41]. Therefore, establishing individualized blood pressure targets, based on patient characteristics, seems reasonable, as suggested by Patel *et al.* [42].

The amount of effort that should be directed towards achieving low blood pressure targets remains a controversial issue, particularly for older and frail patients. Possible adverse events, poly-pharmacy, variable life expectancy, cognitive impairment and a high degree of heterogeneity in comorbidity are factors to consider, according to the 2017 Guidelines of the American Heart Association/American College of Cardiology [14].

Implications for further research

This review demonstrated that there are shortcomings in the definitions, the recording methods and the reporting of serious adverse events. These limitations have made it difficult to interpret and compare the results among studies, particularly the benefit-to-harm ratios.

In general, the majority of all included studies lacked a definition of serious adverse events. Distinct definitions of serious adverse events were only given in two original studies [6,24]. Definitions of specific serious adverse events were provided in the SPRINT study [6] for two adverse events (i.e. AKI and injurious fall), and in the VALISH study [27] for one adverse event (i.e. AKI). A definition of hypotension with cut-off values was not reported in any included study. The SPRINT trial just encoded hypotension as

TABLE 3. Recommendations for recording and reporting of serious adverse event

Manuscript section	Descriptor	Descriptor details
Materials and methods section	Define SAE and each type of SAE	Description of SAE, grading and assessment of SAE
	Define attribution of SAE	Treatment-related or not, decision-process
	Describe collection of SAE-data	How, when, by whom, how many times
Results section	Withdrawal due to SAEs	In each study arm, timing, patient characteristics
	Clear reporting of SAE	Number of patients affected, number for each type of SAEs, patient's achieved BP at time of SAE, recurrent SAEs, grading or severity
Discussion	Balanced discussion of benefits–harms ratio	

SAE, serious adverse event.

symptomatic low blood pressure, but they did not specify low blood pressure cut-offs or symptoms [39]. Nonuniform definitions of individual adverse events and nonuniform documentation methods lead to heterogeneity in the rates and types of reported adverse events. Improved thoroughness in recording and reporting adverse events will most likely lead to higher frequencies of serious adverse events. For example, the rates of dizziness in two studies [23,26] were 0.1 and 53.4%; this large difference was difficult to explain, but it was probably due to more than one issue in methodology. Moreover, we expect that a method of explicitly asking each participant to report adverse events, similar to the method applied in the AASK Trial [23], would most likely result in high rates of serious adverse events.

It was difficult to determine whether an event was related to the antihypertensive treatment; this judgement was made by the trial investigators. No data were provided in any of the included studies that related to making this decision. Two studies provided no information on whether the reported adverse events were treatment related [23,28]. Reporting a discontinuation or change in treatment as a consequence of serious adverse events would be relevant information for physicians.

Future research in the field of target-oriented blood pressure treatment should be conducted with precisely defined outcome(s) and standardized methods for recording serious adverse events. On the basis of our evaluation of the studies in this systematic review, we suggest that future studies should pay careful attention to points listed in Table 3. A more complete discussion and recommendations for the collection and reporting of harms is described by Ioannidis *et al.* [21] in an extension of the CONSORT statement. Further consensus-driven approach could be used to develop study guidelines for recording and reporting SAE in blood pressure treatment based on the input of experts in the field.

Implications for clinical practice

The benefits of intensive antihypertensive treatments include, primarily, reductions in the risks of ischemic heart disease, left ventricular hypertrophy, chronic kidney disease, stroke and intracerebral haemorrhage. Nevertheless, intensive treatment increases the risk of serious adverse events such as hypotension, dizziness, syncope, injurious falls and electrolyte abnormalities, compared with less intensive treatments. Currently, no valid quantitative information is available for physicians, due to the heterogeneous results among published studies. Data are lacking on blood pressure control in patients confined to institutions, patients with symptomatic heart failure and patients with stroke. In the light of our findings, treating physicians must balance the risk of serious adverse events from a too intense treatment with the well documented benefits of lowered blood pressure [17,42,43].

Limitations and strengths

The main limitations of this review were the variable definitions of serious adverse events and the nonuniform recording methods. The main strength of this review is that it was based on the PRISMA guidelines [18] and the SIGN checklists [19], which facilitated a critical evaluation of the included studies. Due to the heterogeneity of definitions and methods for recording adverse events, we could not conduct a synthesis of the results in a meta-analysis. To compensate for this limitation, we provided a detailed, qualitative review of the included studies. Another limitation was that seven post hoc analyses were derived from the same original study, the SPRINT Trial [6]. The results from these studies cannot be considered as independent and therefore do not give the same level of evidence as an original study, but they do contribute useful information as to the risks in different subgroups.

CONCLUSION

Compared with moderate blood pressure treatment, intensive treatment was associated with higher rates of serious adverse events in original studies. Moreover, significantly more treatment-related adverse events were observed in the intensive compared with the moderate treatment group. However, it was difficult to determine whether adverse events could be attributed to the treatment. A quantitative synthesis was not possible due to stark differences in baseline and serious adverse events reporting.

Further research must have precise, uniform definitions of serious adverse events, in general, and of each single adverse event, in particular. The methods of recording and reporting need to be improved and standardized to facilitate the comparison of results.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, *et al.* Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. *Circulation* 2016; 134:441–450.
2. Young JH, Klag MJ, Muntner P, Whyte JL, Pahor M, Coresh J. Blood pressure and decline in kidney function: findings from the Systolic Hypertension in the Elderly Program (SHEP). *J Am Soc Nephrol* 2002; 13:2776–2782.
3. Izzo JL, Levy D, Black HR. Importance of systolic blood pressure in older Americans. *Hypertension* 2000; 35:1021–1024.
4. Egan BM, Zhao Y, Axon R. Us trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. *JAMA* 2010; 303:2043–2050.
5. Cushman WC, Evans GW, Byington RP, Goff DC, Grimm RH, Cutler JA, *et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1575–1585.
6. Sprint Research GroupWright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, *et al.* A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015; 373:2103–2116.
7. Weiss J, Freeman M, Low A, Fu R, Kerfoot A, Paynter R, *et al.* Benefits and harms of intensive blood pressure treatment in adults aged 60 years or older: a systematic review and meta-analysis. *Ann Intern Med* 2017; 166:419–429.
8. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903–1913.
9. Turnbull F, Blood Pressure Lowering Treatment Trialists C. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. *Lancet* 2003; 362:1527–1535.
10. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. *BMJ* 2009; 338:b1665.
11. Cruickshank J, Thorp J, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987; 329:581–584.
12. Alderman MH, Ooi WL, Madhavan S, Cohen H. Treatment-induced blood pressure reduction and the risk of myocardial infarction. *JAMA* 1989; 262:920–924.
13. Merlo J, Ranstam J, Liedholm H, Hedblad B, Lindberg G, Lindblad U, *et al.* Incidence of myocardial infarction in elderly men being treated with antihypertensive drugs: population based cohort study. *BMJ* 1996; 313:457–461.
14. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C, *et al.* 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017; 71:e127–e248.
15. Basu S, Sussman JB, Rigdon J, Steimle L, Denton BT, Hayward RA. Benefit and harm of intensive blood pressure treatment: derivation and validation of risk models using data from the SPRINT and ACCORD trials. *PLoS Med* 2017; 14:e1002410.
16. Bangalore S, Toklu B, Gianos E, Schwartzbard A, Weintraub H, Ogedegbe G, *et al.* Optimal systolic blood pressure target after SPRINT: insights from a network meta-analysis of randomized trials. *Am J Med* 2017; 130:707–719.e8.
17. Chi G, Jamil A, Jamil U, Balouch MA, Marszalek J, Kahe F, *et al.* Effect of intensive versus standard blood pressure control on major adverse cardiac events and serious adverse events: a bivariate analysis of randomized controlled trials. *Clin Exp Hypertens* 2018;1–8.
18. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med* 2009; 6:e1000097.
19. SIGN Scottish Intercollegiate Guidelines Network: Critical appraisal notes and checklists. https://www.sign.ac.uk/checklists-and-notes.html. [Accessed 8 June 2018]
20. ICH Expert Working Group. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Document E2A 1994. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf. [Accessed 18 September 2018]
21. Ioannidis JA, Evans SW, Gøtzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D; CONSORT Group. Better reporting of harms in randomized trials: an extension of the consort statement. *Ann Intern Med* 2004; 141:781–788.
22. Team RC. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2018; http://www.R-project.org/.
23. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, *et al.* Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *J Am Med Assoc* 2002; 288:2421–2431.
24. Accord Study GroupCushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, *et al.* Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010; 362:1575–1585.
25. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, *et al.* Usual versus tight control of systolic blood pressure in nondiabetic patients with hypertension (Cardio-Sis): an open-label randomised trial [Erratum appears in Lancet. 2009 Sep 12;374(9693):880]. *Lancet* 2009; 374:525–533.
26. Study Group SPSBenavente OR, Coffey CS, Conwit R, Hart RG, McClure LA, Pearce LA, *et al.* Blood-pressure targets in patients with recent lacunar stroke: the SPS3 randomised trial. *Lancet* 2013; 382:507–515.
27. Ogihara T, Saruta T, Rakugi H, Matsuoka H, Shimamoto K, Shimada K, *et al.* Target blood pressure for treatment of isolated systolic hypertension in the elderly: Valsartan in elderly isolated systolic hypertension study. *Hypertension* 2010; 56:196–202.
28. Rakugi H, Ogihara T, Goto Y, Ishii M. Comparison of strict-and mild-blood pressure control in elderly hypertensive patients: a per-protocol analysis of JATOS. *Hypertens Res* 2010; 33:1124–1128.
29. Margolis KL, Palermo L, Vittinghoff E, Evans GW, Atkinson HH, Hamilton BP, *et al.* Intensive blood pressure control, falls, and fractures in patients with type 2 diabetes: the ACCORD trial. *J Gen Intern Med* 2014; 29:1599–1606.
30. Beddhu S, Rocco MV, Toto R, Craven TE, Greene T, Bhatt U, *et al.* Effects of intensive systolic blood pressure control on kidney and cardiovascular outcomes in persons without kidney disease. *Ann Intern Med* 2017; 167:375–383.
31. Bress AP, King JB, Kreider KE, Beddhu S, Simmons DL, Cheung AK, *et al.* Effect of intensive versus standard blood pressure treatment according to baseline prediabetes status: a post hoc analysis of a randomized trial. *Diabetes Care* 2017; 40:1401–1408.
32. Cheung AK, Rahman M, Reboussin DM, Craven TE, Greene T, Kimmel PL, *et al.* Effects of intensive BP control in CKD. *J Am Soc Nephrol* 2017; 28:2812–2823.
33. Foy CG, Lovato LC, Vitolins MZ, Bates JT, Campbell R, Cushman WC, *et al.* Gender, blood pressure, and cardiovascular and renal outcomes in adults with hypertension from the Systolic Blood Pressure Intervention Trial. *J Hypertens* 2018; 36:904–915.
34. Obi Y, Kalantar-Zadeh K, Shintani A, Kovesdy C, Hamano T. Estimated glomerular filtration rate and the risk-benefit profile of intensive blood pressure control amongst nondiabetic patients: a post hoc analysis of a randomized clinical trial. *J Intern Med* 2018; 283: 314–327.
35. Still CH, Rodriguez CJ, Wright JT, Craven TE, Bress AP, Chertow GM, *et al.* Clinical outcomes by race and ethnicity in the Systolic Blood Pressure Intervention Trial (SPRINT): a randomized clinical trial. *Am J Hypertens* 2018; 31:97–107.
36. Williamson J, Supiano M, Applegate W, Berlowitz D, Campbell R, Chertow G, *et al.* Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged >75 years a randomized clinical trial. *JAMA* 2016; 315:2673–2682.
37. Jatos Study Group. Principal results of the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS). *Hypertens Res* 2008; 31:2115–2127.
38. Rocco MV, Sink KM, Lovato LC, Wolfgram DF, Wiegmann TB, Wall BM, *et al.* Effects of Intensive blood pressure treatment on acute kidney injury events in the Systolic Blood Pressure Intervention Trial (SPRINT). *Am J Kidney Dis* 2018; 71:352–361.

39. Sink KM, Evans GW, Shorr RI, Bates JT, Berlowitz D, Conroy MB, *et al.* Syncope, hypotension, and falls in the treatment of hypertension: results from the randomized clinical systolic blood pressure intervention trial. *J Am Geriatr Soc* 2018; 66:679–686.
40. Krishnaswami A, Kim DH, McCulloch CE, Forman DE, Maurer MS, Alexander KP, *et al.* Individual and joint effects of pulse pressure and blood pressure treatment intensity on serious adverse events in the SPRINT trial. *Am J Med* 2018; 131:1220–1227.e1.
41. Mezue K, Goyal A, Pressman GS, Horrow JC, Rangaswami J. Blood pressure variability predicts adverse events and cardiovascular outcomes in chronic kidney disease: a post-hoc analysis of the SPRINT trial. *Am J Hypertens* 2018; 31:48–52.
42. Patel KK, Arnold SV, Chan PS, Tang YY, Pokharel Y, Jones PG, *et al.* Personalizing the intensity of blood pressure control modeling the heterogeneity of risks and benefits from SPRINT (Systolic Blood Pressure Intervention Trial). *Circ Cardiovasc Qual Outcomes* 2017; 10:pii: e003624.
43. Bress AP, Kramer H, Khatib R, Beddhu S, Cheung AK, Hess R, *et al.* Potential deaths averted and serious adverse events incurred from adoption of the SPRINT (Systolic Blood Pressure Intervention Trial) intensive blood pressure regimen in the United States: projections from NHANES (National Health and Nutrition Examination Survey). *Circulation* 2017; 135:1617–1628.